REMARKS

Favorable consideration and allowance are respectfully requested for claims 17 and 38 in view of the following remarks.

The rejection of claim 17 under 35 U.S.C. § 102(e) as anticipated by Mauskop (U.S. Patent No. 5,914,129) is respectfully traversed. Claim 17 recites a pharmaceutical formulation which comprises a compound of tramadol hydrochloride and diclofenac sodium. The Office Action incorrectly asserts that claim 17 reads on a composition that contains diclofenac sodium and tramadol hydrochloride. To the contrary, the claim clearly calls for a compound of tramadol hydrochloride and diclofenac sodium.

In particular, claim 17 recites "a compound of tramadol hydrochloride and diclofenac sodium." The claim then continue to describe certain properties related to "said compound", in two different instances. Thus, it is clear that the claim is directed to a compound of tramadol hydrochloride and diclofenac sodium and not simply a mixture of the two active ingredients.

A simple mixture or composition that contains diclofenac sodium and tramadol hydrochloride is not the same as the invention set forth in claim 17. This is a significant difference because it means any reference which merely teaches a mixture of diclofenac sodium and tramadol hydrochloride does not anticipate claim 17.

As evidence of the fact that the compound is formed by the methods taught in the specification, the declaration of Dr. Iris Ziegler is provided as Appendix A to this Reply. As explained in Dr. Ziegler's declaration, a compound of tramadol hydrochloride and diclofenac sodium is formed by the methods described in the present patent application. In this regard, Dr. Ziegler explains that the release rate of both active substances, namely tramadol hydrochloride and diclofenac

sodium, is considerably retarded in the proposed formulation. This lowering of the release rate is achieved without the addition of any retarding agent. A comparison of the results of Test I with the results in Tests II and III in Dr. Ziegler's declaration clearly shows these differences.

Test I shows the release profile of tramadol hydrochloride and diclofenac sodium from pellets containing a compound of these two active substances. As is shown in the chart for Test I, the release rates of the two active substances are nearly the same even over the course of a measured time period from 30 minutes to ten hours. For instance, after ten hours, the total amount of tramadol hydrochloride released is 35 mg, whereas the total amount of diclofenac sodium released is 33 mg.

Test II shows the release profile from pellets that were formed with only tramadol hydrochloride. These pellets were not provided with diclofenac sodium. Compared with Test I, the tramadol hydrochloride only composition of Test II is released much more quickly. In particular, 34.5 mg of tramadol hydrochloride were released after only five minutes, and after 30 minutes, 47 mg had been released.

Test III shows the release profile of pellets formed with only diclofenac sodium. No tramadol hydrochloride was provided in the pellets of Test III. Again, the release profile for the diclofenac sodium only pellets is greatly increased when compared with formulation of Test I which includes the tramadol hydrochloride and diclofenac sodium compound. In particular, after 30 minutes, 46.5 mg of diclofenac sodium had been released from the formulation of Test III.

Thus, the results show that in the pellets comprising the compound of tramadol hydrochloride and diclofenac sodium, the release profile of these two active substances is nearly identical. This is clearly stated in paragraph IV(a) on page 4 of Dr. Zeigler's declaration. Further, the release of these active

substances is significantly delayed in pellets containing the tramadol hydrochloride and diclofenac sodium compound when compared with pellets containing only tramadol hydrochloride or only diclofenac sodium. Dr Zeigler also concludes that the retarded release profile of tramadol and diclofenac in the inventive formulation is caused by the in situ formed compound of tramadol and diclofenac. This conclusion of Dr. Zeigler is provided in paragraphs IV(b and c) on page 4 of her declaration. Finally, Dr. Zeigler concludes that the data demonstrates that the release retardation for both active substances is identical for the inventive in situ compound, without the addition of any retarding agents. See paragraph IV(d) of Dr. Zeigler's declaration.

Since the profiles of the compounds when individually present are nearly identical and the release of these active substances when together as a compound is nearly identical, the total retardation resulting from the active substances being present as a compound is the same for both active substances. This suggests the active substances have formed something greater than a simple mixture. Further, the fact that this retardation is achieved without the addition of any retarding agents also suggests something greater than a simple mixture is being formed.

If, on the other hand, only a simple mixture of the two active substances were present in the pellets of Test I, then the release rate of the active substances would be equivalent to the release rate of the active substances when they are provided alone, for instance in Tests II and III. Because of the significant difference between the release rates shown in Test I with those of Tests II and III, a compound of tramadol hydrochloride and diclofenac sodium has formed, as explained in Dr. Zeigler's declaration.

The Mauskop reference fails to teach a compound of tramadol hydrochloride and diclofenac sodium and accordingly does not teach all of the

limitations of claim 17. Because of this failure to teach all of the elements of the claim, the claim is not anticipated by the reference. Reconsideration and withdrawal of this rejection are respectfully requested.

The rejection of claim 38 under 35 U.S.C. § 103(a) as unpatentable over Mauskop is respectfully traversed. Among other things, claim 38 requires repeating mixing and moistening steps and also requires formulating the mixture under an energy input. Neither of these steps are taught or suggested by the Mauskop reference. The Office Action asserts that repeating the mixing and moistening steps is an obvious variant of the method taught in the reference. To the contrary, there is no teaching or suggestion that it would be of any use or benefit to try to repeat the mixing and moistening steps. Accordingly, one of skill in the art would not be encouraged to try to modify the methods of Mauskop so as to arrive at a method that includes repeating the mixing and moistening steps. Even assuming, *arguendo*, that one of skill in the art contemplated repeating the mixing the moistening steps, such a person would conclude that these steps would provide no additional benefit and, more significantly, would increase the cost of production. Without a perception that this additional step would somehow be of benefit, one of skill in the art would have no motivation to even try such a step. Further, where the step would increase the overall cost of production for the pharmaceutical, a person of skill in the art is even further discouraged from trying such a step.

The Office Action admits that the Mauskop reference does not specifically disclose formulating the mixture under energy input. The Office Action also asserts that compressing or granulating as taught in Remington's Pharmaceutical Sciences amounts to an energy input. However, the claim does not simply require an energy input, rather, the claim requires "formulating the mixture under an energy input." The Office Action does not explain how these methods amount to a step of formulating a mixture under an energy input.

Compressing, for instance, is typically used to form a tablet rather than to form a mixture. The mixture is achieved before any compressing steps. The Office Action provides no indication as to how the methods taught in Remington's Pharmaceutical Sciences could be used to arrive at a method comparable to the method of claim 38 of the present invention.

Despite that even when combined the references fail to teach all of the elements of claim 38, there does not appear to be any motivation provided to try to combine the teachings from Remington's with those of Mauskop so as to arrive at the presently claimed invention. Similarly, there is no motivation to try to modify the teachings of these references so as to arrive at the presently claimed invention.

Because there is no motivation to combine the references, and because even if they were combined they do not teach each and every element of the claimed method, and because there is no motivation to modify the combined teachings of the references, the cited combination does not render claim 38 obvious. Accordingly, reconsideration and withdrawal of the obviousness rejection are respectfully requested.

Claim 17 was provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1 and 11 of co-pending Application no. 10/016,130. Claim 17 of the present application is patentably distinct from the claims of co-pending Application no. 10/016,130. As explained above, a basic requirement of claim 17 is that tramadol hydrochloride and diclofenac sodium are formulated into a compound. In contrast thereto, a basic requirement of the embodiments of Application no. 10/016,130 is that tramadol and diclofenac and/or their respective physiologically compatible salts are present in separate subunits which are each <u>separately</u> formulated. Further, co-pending Application no. 10/016,130 teaches a separation

layer between the two separately formulated sub-units in order to avoid any contact between the two active substances. Because the co-pending application requires separate formation of the two active substances, and the present application requires formation of the two active substances together into a compound, the claims are patentably distinct.

Accordingly, the subject matter of the present claims is not obvious in view of the claims of the earlier application and withdrawal of the provisional obviousness-type double-patenting rejection is respectfully requested.

CONCLUSION

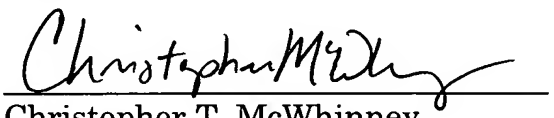
In view of the foregoing, the application is respectfully submitted to be in condition for allowance and prompt favorable action thereon is earnestly solicited.

If there are any questions regarding this amendment or the application in general, a telephone call to the undersigned would be appreciated since this should expedite the prosecution of the application for all concerned.

Although a Petition for an Extension of Time is submitted herewith, if necessary to effect a timely response, this paper should be considered as a petition for an Extension of Time sufficient to effect a timely response, and please charge any deficiency in fees or credit any overpayments to Deposit Account No. 05-1323 (Attorney Docket No. 029310.50932US).

Respectfully submitted,

December 15, 2004



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Appendix A

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANTS: Ziegler et al.
Application NO.: 10/084,676
FILED: 02/28/2002
FOR: ORAL PHARMACEUTICAL FORMS OF ADMINISTRATION WITH A DELAYED ACTION

DECLARATION UNDER 37 C.F.R. § 1.132

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

I, Dr. Ziegler, Iris, hereby declare as follows:

1. I am a citizen of Germany, residing at Im Dickenbruch 4, 52159 Roetgen, Germany,

2. I studied pharmacy at the University Munich (LMU) received a PhD degree in pharmaceutical technology in the year 1996.

3. Since 1996, I have been employed as a research pharmacist in the field of pharmaceutical technology and from 1997 up to now I have been working in this field for the company of Grünenthal GmbH at Aachen, Germany.

4. I am an inventor of the invention disclosed in the US Patent Application Serial No. 10/084676.

5. The following tests were made under my supervision and control:

Test I

Preparation of pellets containing an in situ formed compound of tramadol and diclofenac.

125 g of tramadol hydrochloride, 125 g of sodium diclofenac and 250 g of microcrystalline cellulose (Avicel PH 101, FMC) were homogeneously mixed in a Kenwood Chef mixer for 10 minutes and then granulated with water in an amount sufficient for moistening. The sticky lumpy mass of granules was then extruded in a Nica extruder (type E140) with a 1.0 mm extrusion die. While the rods of extrudate were initially still extremely sticky, they changed in the course of the extrusion process to a very dry extrudate with insufficient plasticity for subsequent spheronization. The extrudate was moistened and granulated again. The resulting granules were extruded again in the Nica extruder and the moist extrudate was then converted to round pellets of uniform size in a Nica spheronizer (type S450). The pellets were dried in a drying cabinet at a temperature of approx. 50°C and fractionated into sieve fractions, ≥90% of the pellets falling within the desired sieve fraction of 800 - 1250 µm.

Composition of the pellets:

Tramadol-HCl	50 mg
Diclofenac -Na	50 mg
Microcrystalline cellulose (Avicel PH 101, FMC)	100 mg
	200 mg

In the pellets produced above the water solubility of the active substances tramadol and diclofenac were both found to be 0.36 mg/ml, determined by the method indicated in the description of the Patent Application Serial No. 10/084676.

The release profile of the in situ compound found of tramadol and diclofenac, determined by the method indicated in the description of the Patent Application Serial No. 10/084676, was as follows:

Time in min	Amount in mg released from 200 mg of pellets	
	Tramadol*	Diclofenac*
30	10	7
120	18	15
300	26	24
600	35	33

* mg released are calculated as mg Tramadol-HCl or Diclofenac-Na in order to compare the released amounts to the incorporated amounts

Test II

Test I was repeated with the exception that Diclofenac-Na was not included in the composition of the pellets.

The release profile was as follows:

Time in min	Amount in mg released from 150 mg of Pellets	
	Tramadol*	
5	34.5	
10	45.0	
15	46.5	
30	47.0	

* mg released are calculated as mg Tramadol-HCl

Test III

Test I was repeated with the exception that Tramadol-HCl was not included in the composition of the pellets.

The release profile was as follows:

Time in min	Amount in mg released from 150 mg of pellets for Diclofenac*
30	46.5
60	48.0

* mg released are calculated as mg Diclofenac-Na

IV. Results:

a.) By preparing pellets containing an in situ formed compound of tramadol and diclofenac at the described ratio, the release profile of tramadol is practically identical to the release profile of diclofenac.

b.) The release of tramadol from pellets containing the inventive in situ compound is much slower than the release of tramadol from pellets containing only tramadol. This retarded release profile of tramadol is caused by the in situ formed compound of tramadol and diclofenac.

c.) The release of diclofenac from pellets containing the in situ compound is much slower than the release of diclofenac from pellets containing only diclofenac. This retarded release profile is caused by the in situ formed compound of the two active substances.

d.) The extent of release retardation for both active substances is identical for the inventive in situ compound without the addition of any retarding agents.

All statements made herein of my own knowledge are true, and all statements made on information and belief are believed to be true, and further, these statements were made with the knowledge that willful false statements and the like, so made, are punishable by fine or imprisonment, or both, under §1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the Patent Application Serial No. 10/084676 or any patent issued thereon.

09. 11. 2004 — I Ziegler

(Date) (Dr. Ziegler, Iris)